Epithelial/mesenchymal heterogeneity of high-grade serous ovarian carcinoma samples correlates with miRNA let-7 levels and predicts tumor growth and metastasis.

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Public Summary:
We studied cells derived in our lab from patient samples. The advantage of patient-derived samples is that they represent the diversity in different patients with ovarian cancer. Many studies use cell lines, which originally came from tumors, but may have been grown in an incubator for decades. In that time, the cells can change from their initial state: they can undergo mutations, their chromosomes may become unstable, and many of the rare cell types originally present may have been lost. Additionally, focusing studies of ovarian cancer on cell lines from a few patients prevents us from learning about the large differences between cells from different patients. We are particularly interested in the differences between samples with regard to the stem cells contained in tumors. We explored these differences in the context of the epithelial-mesenchymal transition, a process that makes cells more aggressive (able to migrate and invade, and thus more able to metastasize). We found that we can classify the patient-derived cells using an EMT score, which measures the gene expression on the RNA level. We also determined the differences in cell morphology or shape, and studied the cell surface molecules that have been shown to act as markers of the stem cell state. Some studies have proposed that the mesenchymal phenotype is associated with stem cell characteristics, but in this study, samples with more epithelial characteristics were more stem cell-like, and were able to form tumors in mice, compared to those that were more strongly mesenchymal. We also studied a small RNA, a microRNA, called let-7, and found that there was an inverse correlation between it and stem cell characteristics. Lower levels of let-7 were associated with the epithelial state, and with sensitivity to cisplatin. Cells with lower let-7 levels were more tumorigenic, but less migratory, and with a lower EMT score, than those with higher let-7 levels. We conclude that let-7 expression and epithelial/mesenchymal state are valuable predictors of ovarian cancer proliferation, in vitro self-renewal, and tumor burden in vivo.

Scientific Abstract:
Patient-derived samples present an advantage over current cell line models of high-grade serous ovarian cancer (HGSOC) that are not always reliable and phenotypically faithful models of in vivo HGSOC. To improve upon cell line models of HGSOC, we set out to characterize a panel of patient-derived cells and determine their epithelial and mesenchymal characteristics. We analyzed RNA and protein expression levels in patient-derived xenograft (PDX) models of HGSOC, and functionally characterized these models using flow cytometry, wound healing assays, invasion assays, and spheroid cultures. Besides in vitro work, we also evaluated the growth characteristics of PDX in vivo (orthotopic PDX). We found that all samples had hybrid characteristics, covering a spectrum from an epithelial-to-mesenchymal state. Samples with a stronger epithelial phenotype were more active in self-renewal assays and more tumorigenic in orthotopic xenograft models as compared to samples with a stronger mesenchymal phenotype, which were more migratory and invasive. Additionally, we observed an inverse association between microRNA let-7 (lethal-7) expression and stemness, consistent with the loss of let-7 being an important component of the cancer stem cell phenotype. We observed that lower let-7 levels were associated with the epithelial state and a lower epithelial mesenchymal transition (EMT) score, more efficient spheroid and tumor formation, and increased sensitivity to platinum-based chemotherapy. Surprisingly, in these HGSOC cells, stemness could be dissociated from invasiveness: Cells with lower let-7 levels were more tumorigenic, but less migratory, and with a lower EMT score, than those with higher let-7 levels. We conclude that let-7 expression and epithelial/mesenchymal state are valuable predictors of HGSOC proliferation, in vitro self-renewal, and tumor burden in vivo.

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